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The Antecedents of Schizophrenia: A Review of Birth Cohort Studies

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Background: **Birth cohort (BC) studies demonstrate that individuals who develop schizophrenia differ from the general population on a range of developmental indices. The aims of this article were to summarize key findings from BC studies in order to identify areas of convergence and to outline areas requiring further research.** ***Method:*** **We define BC studies as studies based on general population BCs where data are collected prospectively from birth or childhood and which identify schizophrenia or related disorders as an outcome. To identify such studies, we searched various electronic databases using the search parameters (schizo* OR psych*) AND (birth cohort). We also checked the references of relevant articles and previous reviews.** ***Results:*** **We identified 11 BCs from 7 countries that have examined schizophrenia as an outcome in adulthood. There is relatively consistent evidence that, as a group, children who later develop schizophrenia have behavioral disturbances and psychopathology, intellectual and language deficits, and early motor delays. Evidence with respect to alterations in language, educational performance, and physical growth has also been identified in some studies. BC studies have also contributed evidence about a wide range of putative risk factors for schizophrenia.** ***Conclusions:*** **BC studies have provided important, convergent insights into how the developmental trajectory of individuals who develop schizophrenia differs from their peers. The combination of new paradigms and larger cohorts, with the tools of modern epidemiology and biomedical science, is advancing our understanding of the developmental pathways to schizophrenia.**

Key words: schizophrenia/birth cohort/epidemiology

Introduction

Subtle deviations in various developmental trajectories during childhood and adolescence can foreshadow the later development of schizophrenia. Studies exploring the antecedents of schizophrenia have used research designs ranging from narrative case studies based on clinical observation, through case control studies, to population-based cohort studies. The latter have included genetic high-risk studies,[1] reconstructed cohorts from archival data,[2,3] military conscript records,[4] and prospectively assessed birth cohorts (BCs). The BC studies were originally designed to explore early health outcomes, but as the cohort members matured a range of adult-onset disorders could also be studied. Thus, over recent decades there has been a shift from retrospective toward prospective studies, from clinical samples toward population-based studies, and from narrowly focussed cross-sectional studies toward detailed longitudinal studies.

The different types of population-based cohort studies, while providing valuable insights into the antecedents of schizophrenia, have various strengths and limitations. For example, young, unaffected individuals have been recruited who are at increased genetic risk of developing schizophrenia (eg, the presence of an affected parent).[5,6] These "high-risk" studies are more economical than general population studies in terms of power (ie, the number of expected cases in the sample) and duration of follow-up (ie, subjects can be recruited in the years prior to maximum risk during early adulthood). However, most people with schizophrenia do not have affected family members[7–9]; thus, results from high-risk studies may not be generalizable.

Studies based on representative, population-based samples provide the ideal sampling frame to quantify the attributable risk associated with various exposures. Studies of military conscripts provide a convenient way to access population-based data, and when linked to mental health registers, such studies can provide insight into the precursors of treated schizophrenia.[10–12] However, these studies are limited with respect to time points (ie, usually one assessment on intake related to fitness for military service in adolescence) and coverage (ie, some conscription-based studies only examine males).

Ideally, population-based cohorts are recruited prior to or soon after birth. Their ability to examine various

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unbiased domains of interest from birth through childhood and adolescence to adulthood can provide unique insights into the changes in developmental trajectories associated with schizophrenia.

The main aim of this article is to summarize key findings from BC studies that have examined the antecedents of schizophrenia. To achieve this, we systematically collated data from the various domains of interest (eg, behavioral, cognitive, etc) to identify areas of consistency and areas lacking in data. We were particularly interested in studies of longitudinal development covering multiple domains. In the second part of the article, we will also provide a concise summary of instances where BC studies had been used to explore putative risk factors for schizophrenia. We conclude by discussing the role of BC studies and developmental epidemiology in informing an integrated model of schizophrenia etiology.

Method

BCs can be defined retrospectively by linking routine administrative datasets. However, for this review, we required that information about cohort members was augmented by additional direct assessments. Thus, to be included in this review, we required that BC studies were based on (a) general population BCs; (b) detailed data collected prospectively from birth, infancy, or childhood; and (c) schizophrenia and related disorders as an outcome.

A broad search string "(schizo* OR psych*) AND (birth cohort)" was applied in MEDLINE (PubMed), PsychINFO, Google Scholar, and Web of Science (including the "Cited Reference Search" system). These databases were searched at the end of May 2008 (details are available from the authors). Potentially relevant articles (in all languages) were reviewed. Citations from relevant articles and review articles were also scrutinized to locate additional relevant articles, book chapters, and conference articles. Additional searches were undertaken based on the names of included BCs.

The results from the BC studies were sorted into 3 primary domains: behavior and psychopathology, cognition (cognitive, language, motor, education), and physical growth. Key features of the included studies were extracted and presented in tabular format.

Results

We identified 11 BCs from 7 countries (see table 1). There were 2 BCs from the United Kingdom, the National Survey of Health and Development (NSHD)[13–15] and National Child Development Survey (NCDS).[16,17] We identified 2 BCs from the United States; the National Collaborative Perinated Project (NCPP) (the New England cohorts[18,19] and the NCPP Philadelphia cohort[20]) and the Perinatal Determinants of Schizophrenia (PDS).[21,22] BCs were also identified from Denmark (Danish Longitudinal Study [DLS],[23,24] and the Copenhagen Perinatal Cohort [CPC],[25,26] Finland (North Finland 1966 Birth Cohort [NFBC_1966]),[27,28] Israel (Jerusalem Perinatal Study [JPS]),[29,30] Dunedin, New Zealand (Multidisciplinary Health and Development Study [MHDS]),[31,32] and Australia (Mater University Study of Pregnancy [MUSP]).[33]

The BCs, which were all based in developed countries, ranged in size from 1037 (the Dunedin cohort) to 68794 (Jerusalem BC). Based on the most recent follow-up with respect to schizophrenia outcomes, we estimate that these studies were based on 2 079 534 person/years.

Most cohorts recruited subjects antenatally of from birth, with the Dunedin MHDS[34] and the Danish DLS[23] prospectively collecting data from later childhood. All used standard but often different diagnostic criteria (table 1); however, there were differences in the definition of the outcome. Some studies defined the outcome as "schizophrenia,"[15,35,36] while other studies used "psychotic symptoms" (NCPP-Providence,[37]) "schizophreniform disorder" (Dunedin MHDS[34,38]), or "screen-positive nonaffective psychosis" (MUSP).[39] Given the differences in the size of the cohorts and the different diagnostic criteria used, the number of cases by last assessment varied from 12 cases of *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, broad schizophrenia in the Providence cohort from the NCPP[40] to 520 cases of *International Classification of Diseases, Ninth Revision,* broad schizophrenia from the JPS.[41] Most studies relied on mental health registers to initially identify cases. Exceptions were the Dunedin BC where a psychiatrist ascertained diagnosis directly by interview and the MUSP which used a questionnaire and the Composite International Diagnostic Interview, computerized version. Some BC studies followed-up with a diagnostic interview of a proportion of the cases (eg, PDS, Susser et al[21]).

Behavioral and Psychopathological Antecedents

We identified 7 articles based on 5 BCs that examined behavioral functioning.[15,34–36,38,39,42] These studies as a group demonstrate that, for many, schizophrenia is associated with a range of behavioral problems during childhood and adolescence.[15,35,36,39,42]

There have been few studies of antecedent psychopathology using BC studies. Important exceptions are the 2 studies from the Dunedin MHDS cohort which identified that responding positively to psychosis-related items can precede schizophrenia[34,38] and a recent study from the MUSP which found that self-reported hallucinations at age 14 can precede nonaffective psychosis.[39]

The exact nature of the behavioral antecedents varies between studies (in keeping with the differences in the measures used in the different cohort studies), but several

broad themes have emerged from this literature. The behavioral antecedents of schizophrenia are subtle. Individuals who later develop schizophrenia are not marked by extreme deviations in behaviors. Also most cohort members with a behavioral feature associated with later schizophrenia do not develop the disorder. In other words, behavioral features have poor positive predictive value.

An advantage of BCs over cross-sectional designs is their ability to report on behavioral changes over time—including sex by age differences. For example, a NSHD study[15] found that schizophrenia was predicted by solitary play preference in childhood and social anxiety by adolescence, while the 2 NCDS studies[36,42] found sex differences in behavioral changes over time. However it appears that, with the exception of the NCPP study[35] and the MUSP study,[39] most studies used mean group differences rather than within-individual change measures to assess behavioral change through childhood and adolescence. For example, the MUSP study,[39] when comparing behavioral measures within the same individual at 5 and 14 years, found a relatively strong association between change measures of "thought disorder" and subsequent nonaffective psychosis. Exploring comparable measures within the same individual over time is better able to describe the direction and "velocity" of trajectories. This information that can be masked when comparing cross-sectional group means. Furthermore, relying on mean group difference may not be the best way to summarize data (eg, if the association is U shaped).

A study of the Dunedin BC was the first to identify that psychotic symptoms at age 11 were strongly predictive of later schizophreniform disorder.[34] A subsequent study of this cohort showed that self-reported psychotic symptoms appeared specific to schizophreniform disorder; they did not predict mania or depression.[38] They concluded that this suggested continuity of psychotic symptoms from childhood to adulthood, rather than adult psychotic symptoms simply being the result of general childhood psychopathology. The MUSP study[39] has also found that self-reported hallucinations (as assessed on the Youth Self Report)[43] during adolescence were significantly associated with increased risk of nonaffective psychosis in young adulthood.

In sum, BC studies have provided relatively consistent evidence that individuals who develop schizophrenia are more likely to have subtle, nonspecific behavioral features compared with their well peers. There is also evidence from 2 cohorts that psychotic-like experiences (particularly hallucinations) may precede schizophrenia by many years.

Cognitive Antecedents

Schizophrenia patients, when considered as a group, show a range of cognitive impairments, some of which predate the onset of psychotic symptoms. BC studies have helped to establish that, for many, schizophrenia is associated with subtle differences in cognitive development during childhood and adolescence. These studies are presented under 4 main headings, intelligence, language and speech, neuromotor, and educational antecedents of schizophrenia.

Cognitive Antecedents: Intelligence

We identified 8 articles based on 6 BCs that examined the issue of intellectual functioning. These studies uniformly found that individuals who develop adult schizophrenia (or schizoaffective disorder, or psychotic symptoms), as a group, achieved lower scores on intelligence tests in childhood and adolescence than their peers,[15,37,44] with some identifying a linear effect rather than subgroup differences.[15,44] BC studies have also generally identified deficits in a range of intellectual impairments covering verbal, nonverbal, and mathematical abilities.[15,37,38,42,44] And in terms of neuropsychological functioning, one study[45] found that schizophreniform disorder was associated with attentional, executive, and motor impairments (but not memory and learning) in early adolescence.

The evolution of intellectual functioning, however, is unclear. While most studies included assessments at a number of ages (thus providing longitudinal assessments of intellectual functioning),[15,37,38,42,44] several areas require further clarification. It is unclear if the longitudinal deficit associated with later schizophrenia is best characterized as stable or declining. For example, while the NCPP Providence study found an IQ decline between ages 4 and 7 years specifically predicted those who developed psychotic symptoms,[37] the NCPP Philadelphia study found IQ lower yet stable between these ages (ie, no intraindividual decline).[44] Examining change at a later age, a CPC study[24] found that both low cognitive function at 12 and 18 years and cognitive decline between these ages increased the risk of schizophrenic disorders. Secondly, it appears that, with the exception of the NCCP Philadelphia study,[44] studies used mean groups differences to assess change over time, rather than assessing intraindividual changes. This may partly explain the differences in findings.

Interestingly, the study by Niendam et al[46] found subtle differences between probands and their unaffected sibs. While probands and their siblings had similar patterns of deficits involving spatial reasoning, verbal knowledge, perceptual-motor speed, and speeded processes of working memory, probands had more severe deficits in perceptual-motor speed and speeded processes of working memory than their unaffected sibs.

Cognitive Antecedents: Speech and Language

Early language dysfunctions have been identified in 4 articles based on 4 BCs. In the British NHSD, preschizophrenia

Table 1. Characteristics of Birth Cohorts

Birth Cohort Name Reference Study a) Details of Cohort b) First "sz" Study	Year(s):Baseline Follow-upAge at Follow-up	Cohort Size: Initial Follow-up	Case ascertainment Case selection criteria	Person/ Years	Incidence[a] Cumulative (%) by Age of Assessment Persons	Domains Covered						
							Cognition					
						Behavior	IQ	Speech	Motor	Education	Growth	Risk Factor
National Survey of Health and Development: England, Scotland, and Wales a) RCOG,[13] Wadsworth[14] b) Jones et al[15]	1946 (3–9 March) 1989 Average age 24 y	5362 sample from 13 687 births F/U = 4746	a) Questionnaire, Mental Health Enquiry, PSE b) *DSM-III-R* criteria applied to material from (a) sz = 30 (20 male, 10 female); controls = 4716	4764	P = 0.63%; M = 0.88%; F = 0.44%	√	√	√	√		√	√
National Child Development Survey: England, Scotland, and Wales a) Shepherd[16] b) Done et al[17]	1958 (3–9 March), 1965, 1969, 1974, 1981, 1985 27 y	1958 = 16 980 F/U 1981 = 12 537	a) Mental Health Enquiry between1974 and 1986 b) Case note review using PSE CATEGO; narrow schizophrenia = 29; broad schizophrenia = 40; 1914 (10%) randomly selected nonpsychiatric controls	51 678	Broad 0.35%; Narrow 0.21%; Crow and Done[129]	√	√	√	√	√	√	√
North Finland 1966 Birth Cohort: North Finland (Oulu and Lapland) a) Rantakallio[27] b) Isohanni et al[28]	1966 second trimester 1994: 28 y1997: 32 y 2001: 34 y	12 058 live born 34 y F/U = 10 569	Various Finnish Registers including Hospital Discharge, Free drug, Pension; Case note review; *DSM-III-R;* 10 458 controls; 111 sz	359 346	0.91%		√		√	√	√	√
National Collaborative Perinatal Project: NCPP New England cohorts; Boston and Providence; Boston, Mass, Providence, RI a) Niswander and Gordon[18] b) Buka et al[19]	1959–1966, 1984–1990 Average age 23 y 1997–2003 Average age ~35 y	New England cohort15 721 offspring7-y F/U = 11 889 Providence only: 4140 offspring F/U = 693	New England cohort (a) screen DIS or record linkage (b) diagnostic interview with SCID; D*SM-IV*, sz = 35; Providence only sample, sz = 12	97 979	Not applicable	√	√	√	√		√	√

Table 1. Continued

Birth Cohort Name Reference Study a) Details of Cohort b) First "sz" Study	Year(s):Baseline Follow-upAge at Follow-up	Cohort Size: Initial Follow-up	Case ascertainment Case selection criteria	Person/ Years	Incidence[a] Cumulative (%) by Age of Assessment Persons	Domains Covered						
							Cognition					
						Behavior	IQ	Speech	Motor	Education	Growth	Risk Factor
NCPP Philadelphia b) Cannon et al[20]	1959–1966, 1985–1996 Average age 32 y	9236 offspring F/U = 8013	Public mental health register; Chart review; *DSM-IV* schizophrenia/ schizoaffective disorder (n = 72); 7941 controls; 88% African American	256 416	2.1%							√
Prenatal Determinants of Schizophrenia: Alameda County, CA a) Susser et al[21] b) Bresnahan et al[22]	1959–1967, 1981-1997 13–38 y	~19 000 F/U = 12 094	Health plan registry; standardized chart review (73% followed up with a direct interview (DIGS); schizophrenia and spectrum disorders (n = 71) (noncases = 12 023)	314 444	sz = 0.35%; SSD = 0.59%						√	√
Dunedin Multidisciplinary Health and Development Study: Dunedin, New Zealanda) a) Silva and Stanton[31] b) Arseneault et al[32]	04/1972–03/1973 Ages 3, 5, 7, 9, 11, 13, 15, 18, 21, and 26 y	1037 (91% eligible; 52% male) 1998–1999 26-y F/U = 972	Direct psychiatric interview of cohort members (DIS-C); schizophreniform, n = 36 (noncases = 936)	25 272	3.7%	√	√	√	√		√	√
Jerusalem Perinatal Study: West Jerusalem a) Davies et al[29] b) Kimhy et al[30]	1964–1976 Average age 35 y	91 459 live births 11 467 with antenatal information 5641 at psychiatric F/U	Cohort Register linked to National Psychiatric Register; broad schizophrenia (including schizophreniform, schizoaffective, schizotypal, delusional disorders, and nonaffective psychoses); *ICD-9* broad sz = 520	197 435	Cumulative incidence per 1000; 0.61% at 25, 0.84% at 30, 0.96% at 34							√
Copenhagen Perinatal Cohort a) Reinisch et al[19]b) Sorensen et al[26]	09/1959–12/1961	9125 births, National University Hospital, Copenhagen	Cohort Register linked to National Psychiatric Register; linkage data collected for adm to1994 *ICD-8*; risk set 7866 individuals, sz = 84	267 444	1.1%						√	√

Table 1. Continued

Birth Cohort Name Reference Study a) Details of Cohort b) First "sz" Study	Year(s):Baseline Follow-upAge at Follow-up	Cohort Size: Initial Follow-up	Case ascertainment Case selection criteria			Person/ Years	Incidence[a] Cumulative (%) by Age of Assessment Persons	Domains Covered						
									Cognition					
								Behavior	IQ	Speech	Motor	Education	Growth	Risk Factor
Danish Longitudinal Study (Project Metropolit): Metropolitan Copenhagena) a) Osler et al[23] b) Osler et al[24]	1953, 200251 y	12 270 male births metropolitan Copenhagenn = 6923 F/u/linkage	Cohort Register linked to National Psychiatric and Conscript Registers (2004)			353 073	1.3%; 1.9%			√				
			ICD-9/10	Original cohort	Males with cogn vars									
			sz	159	87									
			sz spectrum (including sz)	235	133									
Mater University Study of Pregnancy a) Najman[33] b) Welham et al[39]	1981–1983, 2003 Average age 32 y	7223 birthsSE Queensland 21-y F/U = 3801	Questionnaire and CIDI; screen-positive nonaffective psychosis = 60; controls = 3741					√						

Note: The Dunedin cohort recruited subjects at the age of 3 Cannon.[38] F/U, follow-up; PSE, present status examination; *DSM-III-R*, *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised*; DIS, Diagnostic Interview Schedule; SCID, Structured Clinical Interview for *DSM-IV*; *DSM-IV*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;* DIGS, Interview for Genetic Studies; DIS-C, Diagnostic Interview Schedule for Children; *ICD-9*, *International Classification of Diseases, Ninth Revision*; *ICD-8*, *International Classification of Diseases, Eighth Revision*; *ICD-10*, *International Classification of Diseases, Tenth Revision;* CIDI, Composite International Diagnostic Interview, computerized version[130]; SSD, schizophrenia spectrum disorder; sz, schizophrenia

[a]Unless incidence was provided by authors, incidence was calculated from the latest article where sufficient data was given.

Table 2. Birth Cohort Studies of the Behavioral and Psychopathological Antecedents of Schizophrenia

Birth Cohort References	Age (y)	Components	Instrument	Results
NSHD UK1946				
Jones et al[15]	4 and 6	Child's play preference	Mother's structured comments	Solitary play predicted sz (4 y OR = 2.1, CI = 0.9–4.7; 6 y OR = 2.5, CI = 0.8–6.9).
	13	Emotional stability, sociability, negative attitudes to others, and aggression	Self-completed Pintner personality inventory	Self-reported social anxiety had a linear association with sz, no sign effects for aggression, emotional stability, or negative attitudes.
	15	Anxious, antisocial, and abnormal behaviors	Teachers report	Pre-sz children were more anxious in school (linear increase in risk). No association with antisocial behavior. Anxiety (OR = 1.3) and IQ ($P = .009$) independently predicted sz.
NCDS UK1958				
Done et al[36]	7 and 11	Overall scores and scores for overreaction (externalizing behavior) and underreaction (internalizing behavior)	Teacher ratings; Bristol social adjustment guide	Ages 7 and 11: pre-sz boys were overreactive (anxiety for acceptance, hostility, and inconsequential behavior). Age 7 pre-sz girls did not behave abnormally but by 11 were withdrawn (rather than overreactive); age 7: pre-sz children had more social maladjustment ($P < .01$).
Crow et al[42]	7 and 11	Overall scores and scores for overreaction (externalizing behavior) and underreaction (internalizing behavior)	Teacher ratings; Bristol social adjustment guide	Age 7: pre-sz boys were anxious and hostile and showed poor concentration. By age 11 they were also rated as depressed and pre-sz girls as depressed and withdrawn; 7 and 11: pre-szs were hostile and anxious toward other children and adults and show inconsequential behaviors. Little evidence of social withdrawal; by 11: changes in the pre-szs were more striking and include (particularly in females) underreaction/withdrawal; pre-szs were rated restless at 7 (but not 11) and were rated depressed at 11.

Table 2. Continued

Birth Cohort References	Age (y)	Components	Instrument	Results
NCPP_P Philadelphia				
Bearden et al[35]	8 mo and 4 and 7	Social and behavioral	Clinicians (measures not specified)	Deviant behavior predicted sz at 4 (OR = 1.68, 1.14–2.46) and 7 (OR = 1.65, 1.13–2.41) (controlling for age, sex, race, parental education, and SES); rate of sz steeply increased with the number of deviant behaviors shown at 4 and 7; at 7, social maladjustment predicted sz.
MHDS, Dunedin, New Zealand				
Poulton et al[34]	11	Delusions and hallucinations	Structured diagnostic interview	Self-reported psychotic symptoms at 11 predicted schizophreniform disorder (OR = 16.4, 3.9–67.8); attributable risk; 42% of schizophreniform group reported one or more psychotic symptoms.
Cannon et al[38]	5, 7, 9, and 11	Internalizing and externalizing emotions and behaviors in past year	Parental and teachers; Rutter Child Scales	Schizophreniform group showed more internalizing problems and strong trend for externalizing problems (adjusted for sex and SES)
	5, 7, 9, and 11	Social isolation and peer rejection	Parental questions	Schizophreniform group were more likely to experience social rejection.
	11	Psychotic symptoms	Child psychiatrist; DIS-C	Schizophreniform disorder was associated with the strong-symptom group (OR = 16.4, 3.9–67.8) and the weak-symptom group (OR = 5.1, 1.7–18.3).
MUSP, Brisbane, Australia				
Welham et al[39]	5, 14	General psychopathology, "Thought disturbances;" hallucinatory experiences at 14	Achenbach Scales; CBCL (mother's rating) 5 and 14; YSR (self-rating) 14	Screen-positive nonaffective psychosis was associated with —general psychopathology in males at 5 and 14 and females at 14 only —high psychopathology at both 5 and 14 in one group of males —high psychopathology at 14 only in another group of males and a group of females —self-reported hallucinatory experiences at 14 for males and females

Note: NSHD, National Survey of Health and Development; OR, odds ratio; CI, confidence interval; NCDS, National Child Development Survey; SES, socioeconomic status; sz, schizophrenia; MHDS, Dunedin Multidisciplinary Health and Development Study; DIS-C, Diagnostic Interview Schedule for Children; MUSP, Mater University Study of Pregnancy; CBCL, Child Behavioral Checklist; YSR, Youth Self Report.

Table 3. Birth Cohort Studies of Intellectual Functioning as an Antecedent of Schizophrenia

Birth Cohort Name Studies	Specific Methods			Results
	Ages (y)	Components	Instruments	
NSHD UK1946				
Jones et al[15]	8	Nonverbal, verbal, reading, and vocabulary	Not specified	For all ages pre-sz mean scores were consistently lower, with significant linear trends. Verbal, nonverbal and mathematical deficit > vocabulary and reading (adjusted for sex and social class). Risk was not confined to very low scores. effect size
	11	Nonverbal, verbal, reading, arithmetic, and vocabulary		
	15	Nonverbal, verbal, reading, and arithmetic		
NCDS UK1958				
Done et al[36]	7	Reading and mathematics	Southgate word recognition test	From age 7, pre-sz showed a range of intellectual impairments: eg at 16 pre-szs had poor English, reading, spelling, and mispronouncing words ($P < .001$).
	11	General verbal and nonverbal intelligence	GAT and Reading Comprehension test.	
	16	Reading and mathematics	Reading Comprehension test; Mathematics tests = age appropriate	
NCPP_RI				
Kremen et al[37]	4	General intelligence	Stanford-Binet	Increased risk of adult psychotic symptoms for those with IQ declines between ages 4 and 7 (OR = 6.62, 95% CI = 2.52–17.42).
	7	General intelligence	WISC (abbreviated version)	
NCPP_P Philadelphia				
Cannon et al[44]	4	General Intelligence Scale	Stanford-Binet (overall score)	Ages 4 and 7: pre-sz performed worse (linear effect) on verbal and nonverbal tests. effect size
	7	Full score, verbal, and nonverbal	WISC (10 subtests)	
Niendam et al[46]	7	Spatial reasoning, verbal knowledge, perceptual motor speed, and speeded processes of working memory	WISC (7subtests)	Pre-sz group showed deficits involving spatial reasoning, verbal knowledge, perceptual-motor speed, and speeded processes of working memory.
MHDS, Dunedin, New Zealand				
Cannon et al[38]	3	Verbal comprehension	Peabody Picture Vocabulary Test (language)	At all ages (from 3 to 11) schizophreniform group performed more poorly (about 0.4 SDs) on standard IQ tests
	5	General intelligence	Stanford-Binet	
	7, 9, and 11	General intelligence	WISC–revised	
Cannon et al[45]	13	Included motor, attention, executive, memory, and learning ability	Battery of standard neuropsychological tests	Schizophreniform disorder was associated with attentional, executive and motor impairments (but not memory and learning at age 13.
DLS Copenhagen Denmark				
Osler et al[24]	12	Subtests: spatial, arithmetic, and verbal	Härnquist test (part of school questionnaire in 1965)	Low cognitive function at 12 and 18 years and cognitive decline between these ages were associated with increased risk of schizophrenic disorders.
	18	4 categories: letter matrices, verbal analogies, number series, and geometric figures	Børge Priens cognitive test, taken at conscription, 90% of cohort members attended 1972–1973.	

Note: NSHD, National Survey of Health and Development; sz, schizophrenia; NCDS, National Child Development Survey; GAT, General Achievement Test; WISC, Wechsler Intelligence Scale for Children; OR, odds ratio; MHDS, Dunedin Multidisciplinary Health and Development Study; DLS, Danish Longitudinal Study.

Table 4. Birth Cohort Studies of Speech and Language Functioning as Antecedents of Schizophrenia?

Birth Cohorts Studies	Specific Methods			Results
	Ages (y)	Components	Instruments/Analyses	
NSHD UK1946				
Jones et al[15]	2, 6, 7, 11, 15	Speech acquisition and quality	Health visitor/physician records	Speech delay at 2 y; up to age 15, cases had more speech problems than controls (OR 2.8 (0·9–7·8), $P = .04$)
NCDS UK1958				
Crow et al[42]	7	Speech acquisition and quality; oral or reading	Parental and teacher assessment	Parents rated pre-sz speech acquisition and quality as normal. Teachers rated pre-sz speech and reading as poor.
	11	Speech, English	Teacher assessment	Teachers rated pre-sz speech as poor.
NCPP Philadelphia				
Bearden et al[35]	7	Receptive and expressive language; speech intelligibility; language ability	Speech pathologist assessment; Auditory-Vocal Association Test	Abnormal speech predicted adult sz (OR = 12.70 95%CI = 2.46–65.66); language performance was negatively associated with sz (OR = 0.71, 95% CI = 0.57–0.89).
MHDS, Dunedin, New Zealand				
Cannon et al[38]	3 and 5	(All ages) Receptive and expressive language	Reynell Developmental Language Scales	All ages: schizophreniform group receptive (but not expressive) language was significantly poorer than controls (between 0.2 and 0.6 SDs).
	7 and 9		Illinois Test of Psycholinguistic Abilities	Various adjustment including OCs had little effect.

Note: NSHD, National Survey of Health and Development; OR, odds ratio; NCDS, National Child Development Survey; CI, confidence interval; DMHDS, Dunedin Multidisciplinary Health and Development Study; OCs, obstetric complications.

children were found to have subtle speech differences by the age of 2, and up to age 15, they had more speech problems.[15] In the NCDS study, parents rated pre-schizophrenia speech as normal at age 7, while teachers' rated their oral and reading ability at age 7 and speech at age 14 as poor.[42] It is less clear if expressive or receptive language is most disordered. For example, the NCPP study[35] found childhood poor speech and expressive language predicted schizophrenia-schizoaffective disorder, whereas in the Dunedin cohort, Cannon et al[38] found that throughout childhood receptive rather than expressive language predicted schizophreniform disorder. Several studies had repeated measures of speech and language at various ages and were able to report on continuity. For example, the NSHD study found that pre-schizophrenia was not associated with grossly abnormal speech in adolescence; they had apparently caught up.[15]

Cognitive Antecedents: Neuromotor Dysfunction

We found 6 articles based on 5 BCs that examined neuromotor functioning. These studies uniformly found that deficits in infant motor development (IMD) and/or motor coordination were associated with schizophrenia in adulthood. Some studies examined age at attaining motor milestones in infancy.[15,47] For example, the NFBC_1966 study found a linear effect where earlier milestones attainment reduced and later milestones attainment increased the risk.[47] Other BC studies covered IMD and/or motor coordination in later childhood, adolescence, or adulthood.[15,38,42,48,49] Interestingly, the NFBC_1966 study[48] which found that early developmental deviation capacity in the first year of life was associated with lower school performance at age 16 also found that developmental continuity in children who developed psychoses was stronger, ie, less flexible, than among normal. However, Rosso et al[49] found that motor coordination deviance at age 7 predicted both adult schizophrenia and unaffected sib status, while unusual movements at ages 4 and 7 predicted adult schizophrenia but not unaffected sib status (perhaps then specific to the clinical phenotype). Also preschizophrenia children did not show expected developmental decline in unusual movements, which the authors thought may reflect aberrant functional maturation of cortical-subcortical pathways.

All studies included multiple premorbid assessments and found evidence of a continuity of motor deficits in schizophrenia—and between differing measures of motor function—infant developmental milestones (ie IMD),

Table 5. Birth Cohort Studies of Neuromotor Dysfunction as an Antecedent of Schizophrenia

Birth Cohort Study	Specific methods			Results
	Ages (y)	Components	Instruments/Analyses	
NSHD UK1946				
Jones et al[15]	2	Age at sitting, standing and walking alone	Health visitor/physician records	Motor development (sitting, standing, walking, teething, talking) attained later in cases, particularly walking (difference in means 1.2 mo, $P = .005$). No effect for age at attainment of bladder and bowel control.
NCDS UK1958				
Crow et al[42]	7	Neuromotor function recorded at each age (eg walking backward, heel-to-toe standing)	Parental assessment	Age 7: pre-sz were slow to develop continence and showed poor coordination and vision. ($P < .01$).
	11		Medical officer	Age 11: no impairment in vision and motor coordination but they were more likely than controls to be recorded as incontinent.
	16		Medical officer	Age 16: rated clumsy. ($P < .01$).
NFBC_1966				
Isohanni et al[47]	1	Learned to stand, walk, and speak; Attained bladder and bowel control	Health visitor/welfare centers	Found a linear effect where earlier milestones reduced, and later milestones increased the risk of sz.
Isohanni et al[48]	1	Learned to stand, walk, and speak; Attained bladder and bowel control.	Health visitor/welfare centers	Compared with earlier learners, late learning to stand in pre-sz/any psychosis was associated with poor school performance (motor and theoretical domains)
	16	School performance	Generalized linear modeling	
NCPP_Philadelphia				
Rosso et al[49]	8 months	Unusual movements = eg athetoid movements, head not erect/unsteady	Standardized psychological and neurological examinations	Unusual movements (at ages 4 and 7) and motor coordination (at age 7) increased the risk of sz. Pre-sz children did not show expected developmental decline in unusual movements.
	4	Tremors, tics, spasms, or athetoid movements		
	7	Ditto plus with tests of gross and fine motor coordination		
MHDS, Dunedin, New Zealand				
Cannon et al[38]	3	Age attaining developmental milestones (smiling, sitting up, walking, continence, fed self, talked words and sentences).	Maternal retrospective recall, Bayley Motor Scales, Pediatric neurologist	Pre-szF began to walk later (adjusted for sex and SES) -no differences for other infant milestones.
	5	Motor development (eg motility, passive movements, reflexes, facial musculature, strabismus, nystagmus, foot posture, and gait)	McCarthy Motor Scales	Age 3: pre-szF (but not other psychiatric groups) was more likely to have one or more neurologic signs (OR 4.6).
	7 and 9		Basic Motor Ability Test	Ages 3, 5, and 9 (not 7) pre-SzF had poorer motor skill.

Note: NSHD, National Survey of Health and Development; NCDS, National Child Development Survey; sz, schizophrenia; NFBC, North Finland 1966 Birth Cohort; MHDS, Dunedin Multidisciplinary Health and Development Study; SES, socioeconomic status; OR, odds ratio; szF, schizophrenia females.

Table 6. Birth Cohort Studies of Educational Performance as an Antecedent of Schizophrenia

Birth Cohort Studies	Ages (y)	Components	Instruments/Analyses	Results
NCDS UK1958				
Crow et al[42]	7	Reading, English, number work, and book use	Teacher assessment	Teachers rated pre-sz reading ability as well as English, number work, and book use as poor.
NFBC_1966 Finland				
Isohanni et al[52a]	14	Class level (normal, age appropriate vs below age level/special school)	School and diagnostic data from national registers	Age 14 children not in their normal grade/normal school had a 2–8 times higher risk of mental disorders.
	16	School marks		Lower school marks did not predict sz or other psychoses (but did predict nonpsychotic disorders).
Isohanni et al[53a]	16	School marks	School and diagnostic data from national registers	Eleven percent of pre-sz boys had excellent school marks compared with only 3% for comparisons (adjusted OR 3.8; 95%CI 1.6–9.3).
Isohanni et al[131]	Various ages	Educational outcome (completion of basic, upper secondary, or tertiary) stratified by age at onset (early onset <22 y v later)	School and diagnostic data from national registers	Early sz and nonpsychotic cases had a 3- to 6-fold adjusted odds for attaining only a basic educational level. However, persons with a later psychosis onset performed nearly as well as comparisons.
Alaräisänen et al[54]	16	School performance (school marks)	National registers based on teacher assessment	In psychosis having good school performance (top 20%) was associated with a higher risk of suicide (adjusted hazard ratio 3.56 (0.97–13.05).
	By 35	Rates of suicide	National registers	In nonpsychosis, there was no association.

Note: NCDS, National Child Development Survey; sz, schizophrenia; NFBC_1966, North Finland 1966 Birth Cohort; OR, odds ratio; CI, confidence interval.
[a]28-year follow-up (sz = 76); rest later follow-up.

and later childhood motor functioning. For example, in the early UK study[15] probands did not show grossly abnormal motor behavior in adolescence, they had largely caught up. Further studies based on the NFBC_1966 found continuity between IMD and poor adolescent school performance in motor domains, while the pattern of association between development and adult cognition was broadly similar in schizophrenia and the general population.[50] Similarly in the Dunedin cohort, children who subsequently developed schizophreniform disorder had persistently poor motor function over repeated measurements in childhood.[38] Interestingly, 2 other BC studies (not included in the table) have found similar associations between IMD and cognitive performance/brain morphology in the adult nonpsychosis cohort.[45,51] The latter study[51] also found that the normal relationship between infant development at age 1 and adult brain structure 34 years later is disturbed in schizophrenia (''developmental dysmetria'').

Cognitive Antecedents: Educational Performance

We found that 5 articles based on 2 BCs have examined the issue of educational performance as an antecedent of schizophrenia. While a number of school-related risk factors for developing schizophrenia have been identified (repeating a grade, difficulties completing the final school level, and school marks), results have produced mixed or unreplicated findings. In the early NCDS study, poor educational performance had a linear association with schizophrenia. This effect was not confined to those with lowest IQ and was independent of behavior, apparent by age 8 as a general dysfunction, and possibly increased thereafter.[15] However, in the NFBC_1966, 14-year-olds who were below their expected normal grade

(as predicted by age) had a higher risk of developing schizophrenia, but low school marks did not predict schizophrenia.[52] Interestingly, good school performance may also be associated with later schizophrenia. A NFBC_1966 study found that 11% of boys with premorbid symptoms had excellent school marks compared with 3% in the healthy population.[53] Also, Alaräisänen et al[54] found that good school performance at age 16 was associated with increased risk of suicide (before age 35) in persons who develop psychosis, while for those who do not develop psychosis, it is associated with lower suicide risk. Interestingly, studies of the general population of the NFBC_1966 have also identified developmental continuity between age of IMD and educational performance at age 16 and 31[55,56]: (ie, those who develop faster during their first year of life tend to attain higher levels of education in adolescence and adulthood).

In sum, BC studies have provided relatively robust evidence that individuals who later develop schizophrenia show early deviation on a range of cognitive measures related to intelligence, motor development, speech and language, and educational outcomes. The importance of examining the longitudinal course of cognition in schizophrenia has been highlighted by a recent meta-analysis.[57]

Physical Growth and Puberty

We identified 9 studies based on 7 BCs that examined physical growth, with 2 including pubertal maturation. Low birth weight and/or being small for gestational age (SGA) can be conceptualized as indices of fetal growth retardation (which may be a proxy marker for more widespread impairment of physical development) or independent risk-modifying factors. Measures related to birth anthropometry were reported in 8 studies from 6 countries. Results were mixed with 3 reporting that low birth weight or being SGA increased the risk for adult schizophrenia, while 4 failed to find such an effect. Interestingly, a BC study based on the NCPP[58] found that low birth weight (along with hypoxia) was associated with poorer cognitive functioning of cohort members at age 7. Other variables related to possible fetal growth retardation, such as birth length and head circumference, have received little attention. However, the UK NCDS study[42] found that head circumference at birth did not predict later schizophrenia.

Concerning anthropometric measures during childhood and adolescence, studies based on the 2 UK BCs, the NHSD and NCDS, found no association between childhood height, weight, and future schizophrenia.[15] Similarly, in the NHSD, head circumference at age 7 did not predict schizophrenia.[42] However, a male-only study from the CPC[59] found that body mass index rather than height at age 18 predicted subsequent schizophrenia. A recent PDS study[60] is the first BC study to examine the growth trajectory in schizophrenia. They found that early growth in schizophrenia spectrum disorder was slower during early life for females but not for males.

Two BC studies have reported on pubertal maturation (NSHD[15]; NCDS[42]). Neither study found an association between pubertal maturation and later schizophrenia. In sum, there is a relative paucity of BC studies of growth and maturation from infancy to adulthood, with only one study examining a growth trajectory.[60]

BCs and the Exploration of Risk Factors for Schizophrenia

The first section provided a systematic review of neurodevelopmental processes from the perspective of antecedents of schizophrenia. By studying the progression of the preclinical ''phenotype'' associated with schizophrenia, researchers hope that deviations in the expected trajectory of development may reveal vulnerability mechanisms that impact on these pathways. The second part of the article provides selected examples of studies that use BCs to explore more specific research questions (eg, risk factors related to susceptibility, risk factors that impact on the subsequent course of the illness, etc). The taxonomy of BC studies is by no means distinct, and studies in both sections share common conceptual frameworks.

BCs play an important role in exploring candidate risk factors associated with schizophrenia and thus have complemented data from other research designs. The potential effect of various pregnancy and delivery complications has been the topic of 6 studies based on 5 BCs (the NCDS 1958[17,61]; the NFBC_1966[62]; cohorts from the NCPP[40,44]; and the Dunedin MHDS[38]). Two of these studies,[61,62] along with other population-based studies, were subject to a meta-analysis resulting in a modest effect size of about 2.[63] However, the NFBC_1966 study found that a stringent definition of severe delivery complications led to a larger effect: schizophrenia was 7 times as common in those exposed to perinatal brain damage.[62]

Paternal age has been examined in 2 BC studies (JPS[41] and PDS),[64] with both finding that older paternal age at the birth of the offspring increases the risk of schizophrenia; while Kimhy et al[30] in the JPS study found that much of an association between maternal household crowding during pregnancy and the offspring's risk of schizophrenia was explainable by the impact of paternal age. BC studies have also examined the effect of the mothers' behavior during pregnancy. For example, 2 BCs have reported on the effects of the mother's mental health and lifestyle as a risk for schizophrenia: while studies of the NFBC_1966[65] and NCDS[15] found an increased risk for schizophrenia in the offspring of antenatally depressed mothers. Significantly, an early study of the NCDS[61] found that increased risk of OCs in schizophrenia may result from maternal physique/lifestyle rather than environmental factors or delivery complications.

Table 7. Birth Cohort Studies of Physical Growth and Pubertal Maturation as an Antecedent of Schizophrenia

Birth Cohort Studies	Ages (y)	Components	Instruments/Analyses	Results
NSHD UK1946				
Jones et al[15]	0, 7, 11	Height and weight	Medical assessments	Pre-sz and controls did not differ in BW or height and weight at 7 or 11.
		Age at puberty	Medical assessments	Pre-sz and controls did not differ for age at puberty.
NCDS UK1958				
Crow et al[42]	0, 7, 11, 16	Height and weight	Medical assessments	Pre-sz and controls did not differ in BW, height, and weight at 7, 11, or 16, or HC at age 7.
	11, 16	Various indices of pubertal development	Medical assessments	Pre-sz and controls did not differ for pubic hair, genital/breast development (age 11) or for pubic hair, menarche, and age of voice change (age 16).
Sacker et al[61]	Birth	Maternal—physical/lifestyle/ demographics; history/ current obstetrics; condition of baby.	Medical assessments	Low BW increased the risk of sz (OR 3.89, 1.86–8.14) (though usually full term).
NFBC				
Jones et al[62]	Birth	Birth weight (and other PBCs)	Medical records	Low BW increased the risk of sz (<2500 g, OR = 2.6, 1.1–5.9);<2000 g OR = 6.2, 1.9–20.3); low BW and short gestation increased the risk of sz (<37 wk, OR 3.4, 1.2–9.4)
NCPP_P				
Cannon et al[44]	Birth	Birth weight (and other PBCs)	Public health database, *DSM-IV* diagnoses via medical record review	BW was not associated with sz (but hypoxia-associated OCs were).
Bearden et al[35]	8 mo and 4 and 7	Birth weight (and other PBCs)	Medical records	Low BW (a) did not increase risk of sz or (b) interact with social/behavioral problems or speech/language performance in pre-sz.
PDS				
Perrin et al[60]	Birth, 9	Height, weight, and BMI	Physical measures	For females, growth in SSD was approximately 1 cm/y slower during early life ($P < .01$); no association was found for males. While there was no effect for later childhood growth and weight, slower change in BMI was associated with SSD.
MHDS, Dunedin				
Cannon et al[38]	Birth	Birth weight <2500 or >4 kg; gestational age ≤37 or >41 wk; small or large for gestational age	Examination at birth; prenatal details from hospital records.	SGA status (OR, 2.8) (as well as low Apgar score (OR 5.9) and hypoxia at birth (OR 5.0) increased the risk of schizophreniform disorder.

Table 7. Continued

Birth Cohort Studies	Ages (y)	Components	Instruments/Analyses	Results
CPC Copenhagen, Denmark Sorensen et al[59]	Birth, 1, 9, and18	Height, weight, and BMI	SES from medical records (age 1); physical measures at conscription (age 18)	Mean BMI of pre-sz young men was lower than average (independent of maternal prepregnancy BMI, parental social status, birth weight, and length). No case-noncase difference for mean height.

Note: NSHD, National Survey of Health and Development; sz, schizophrenia; BW, birth weight; NCDS, National Child Development Survey; HC, healthy control; OR, odds ratio; NFBC, North Finland 1966 Birth Cohort; NCPP_P, NCPP Philadelphia; PBC, pregnancy and birth complications; OC, obstetric complications; *DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; PDS, Perinatal Determinants of Schizophrenia; BMI, body mass index; SSD, schizophrenia spectrum disorder; MHDS, Dunedin Multidisciplinary Health and Development Study; SGA, small for gestational age; CPC, Copenhagen Perinatal Cohort; SES, socioeconomic status.

Two related findings are studies from the CPC (Sorensen et al[26]) where offspring of mothers having hypertension and/or having diuretic treatment during pregnancy had a 4-fold increased risk of developing schizophrenia (maternal schizophrenia led to a 11-fold increase) and where early weaning was associated with an increased risk of schizophrenia (adjusted odds ratio [OR] = 1.73 with 95% confidence interval = 1.13–2.67).[66]

A surprisingly wide range of early life exposures have been examined in BCs, which range from dry cleaning fluid[67] and analgesics[68] to nutritional deficiencies and infectious agents. With respect to prenatal nutrition, homocysteine, a marker of folate of metabolism, was found to be significantly elevated in the third trimester sera from mothers of individuals with schizophrenia.[69,70] Developmental vitamin D deficiency, a candidate risk factor that might underlie the season of birth effect[71] has been examined in 2 BCs. Absence of vitamin D supplementation was associated with an increased risk of schizophrenia in males in the NFBC_1966,[72] and a trend level association between very low maternal vitamin D and an increased risk of schizophrenia was identified in NCPP-Providence sample.[73] With respect to prenatal infection, studies based on the PDS have reported an association between schizophrenia and (a) rubella[74] and (b) various respiratory infections (including influenza).[75] Archived biological samples from BCs have also helped to clarify the ambiguous associations between prenatal infection and schizophrenia found at ecological studies (reviewed by Brown and Susser[76]). Based on banked sera, increased risk of schizophrenia/psychosis has been associated with prenatal exposure to influenza,[77] genital and reproductive infections (PDS),[78] *Toxoplasma gondii*,[70] and herpes simplex virus type 2.[79] However, a subsequent PDS study failed to confirm the specific finding on IgG and herpes simplex virus type 2.[80] While most studies have focus of prenatal exposure, cerebral infection in childhood may also be a risk for later schizophrenia.[81,82]

With respect to psychosocial risks factors, a study based on the NFBC_1966 reported that the risk of later schizophrenia among ''unwanted children'' showed a 2.4-fold increase compared with wanted or mistimed children.[83] This finding has received some support from a PDS study.[84] However, there is mixed evidence on whether separation from parents presents a risk. In the NCDS,[42] preschizophrenia children were more likely to have been in care, experienced parental separation, or loss or been referred to a specialist for emotional problems.

Similarly there is mixed evidence from cohort studies based on various designs on whether low, medium, or high socioeconomic status (SES) in the family of origin presents an increased risk of schizophrenia (reviewed by Bresnahan et al[85]). Studies of BC have produced some interestingly findings. For example, an early study from the NSHD UK1946[15] found no association between

schizophrenia and low social class (or urban/rural birth or population size of place of birth). A later NFBC_1966 study[86] found that schizophrenia was associated with the father's higher social class (interestingly, these fathers often also showed serious psychopathology, especially alcoholism). Consistent findings of higher rates of schizophrenia in migrants and urban areas have highlighted that social risk is more complex than SES per se.[87] Curiously, Bresnahan et al[88] have recently examined the relationship between ethnicity and the incidence of schizophrenia in the PDS—a higher incidence of schizophrenia was found in the African American cohort members, which was still significant after controlling for family SES.

Aspects of early rearing may also present a risk for schizophrenia. For example, an effect has been found for birth order in the NFBC[89] and for disturbances in parent-child relationships in the NSHD UK1946 BC[15] and in the Dunedin MHDS BC.[38] Other family-related factors have not shown an association with schizophrenia in NFBC_1966 studies, such as living in a single-parent family[90] or being a member of a large family.[91] While not necessarily arising from within the family, childhood abuse as a risk factor has recently received increased attention as a risk factor for schizophrenia.[92,93] As far as we are aware, this topic has not been examined in a BC study.

Various exposures during later childhood or adolescence may also constitute risks for schizophrenia. For example, in the NFBC_1966, Riala et al[94] found that initiation of smoking may signal the prodromal phase of schizophrenia. BC studies are also providing evidence that cannabis use is an independent risk factor for schizophrenia. A study based on the Dunedin cohort found cannabis use at age 15 and 18 increased the risk of psychotic symptoms or schizophreniform disorder at age 26 (with an OR = 11.4 for those using cannabis before age 15).[95] No association was found for other substances. Importantly, they also assessed the presence of psychotic symptoms at age 11 and found that the cannabis use and increased psychosis-risk association was independent of preexisting psychotic symptoms. Another New Zealand–based BC (the Christchurch Health and Development, which has not yet included schizophrenia as an outcome measure) found daily users of cannabis had rates of psychotic symptoms that were between 2.3 and 3.3 times higher than those for nonusers.[96] Although the evidence from the prospective cohort studies suggests a possible causal link between cannabis use and psychosis, most people who smoke cannabis do not develop schizophrenia. A gene-environment interaction has been proposed, with some individuals being genetically vulnerable to the effects of cannabis.[97] A study using the Dunedin BC tested this hypothesis and found that a functional polymorphism of the *catechol-O-methyltransferase* (COMT) gene moderated the influence of adolescent cannabis use on adult psychosis.[98]

Finally, BCs can provide convenient platforms for the exploration of a range of factors related to schizophrenia outcomes and comorbidity. For example, one study found seasonality in schizophrenia admissions,[99] and another associated duration of first hospitalization with risk of readmission.[100] A number of NFBC_1966 studies have examined comorbid physical disorders[101] and mortality risk.[102] More recent studies have targeted lipid levels and medication,[103] metabolic syndrome,[104] and weight gain.[105] Other studies have examined clinical and psychosocial sociodemographic correlates of schizophrenia.[106,107] BC studies have also been involved in studying brain morphology and function in schizophrenia. For example, an early NSHD UK1946 study of laterality[108] found that at age 11 preschizophrenia cohort members had excess left eye dominance. A later NFBC_1966 study[109] found no differences between schizophrenia groups and controls in hippocampus and amygdala characteristics. The use of BCs to examine the course and outcome of schizophrenia will be the subject of a future review article.

Discussion

BC studies have identified subtle developmental deviances from infancy, through childhood and adolescence into adulthood in many individuals who develop schizophrenia. The behavioral, motor, and neurocognitive antecedents of schizophrenia have been documented in several independent studies. BC studies have also contributed evidence about a wide range of putative risk factors for schizophrenia. These studies generally support findings on antecedents made by studies based on other designs—such as high-risk studies.[110,111]

In general, the antecedents of schizophrenia are subtle in terms of the effects estimated from measures available in most BC studies. Those who develop schizophrenia do not form a readily identifiable subgroup but tend to have a slight shift in distribution of the variable of interest.[15] Thus, these measures have weak positive predictive value.[110] However, predictive value depends on prevalence; for rare disorders, such as schizophrenia, trying to distinguish early instances of premorbid symptoms from the general population is difficult.[55] Nevertheless small, nonspecific effects are common to most genetic and environmental risk factors for complex diseases.[112] Nonspecificity could mean that intervention to reduce childhood behavioral or neurocognitive dysfunction could avert a range of disorders—including schizophrenia.[15] This is borne out by the Dunedin cohort finding that 75% of adults with a psychiatric disorder had a diagnosable disorder as children.[113]

The precise nature of the deviations is not always shifted toward impairment. Some researchers have suggested that deviations from the norm in either direction (ie, either inferior or superior performance) may be risk

factor for schizophrenia.[110] Furthermore, the division between antecedents as passive risk indicators vs active risk–modifying factors is somewhat artificial. They may be better conceptualized as interactive domains leading to a developmental cascade.[114,115]

BC studies have important limitations. For example, like any observational study, participants are not randomly assigned to exposures; thus, any observed associations may be confounded by an unmeasured factor (ie, residual confounding). Also, there is a lengthy lag between the initiation of the BC and the age when schizophrenia becomes clinical prominent.[116] In fact, we found that many BCs are ''young''—cohort members would not have passed through their full period of risk for schizophrenia. For example, while the UK BCs age at follow-up was 43 years, the MUSP age at follow-up was 21 years. This generally results in a limited number of cases and reduced power to detect associations particularly when stratified by sex and controlling for confounding effects. In addition, because the cohorts require decades of follow-up in order to examine schizophrenia, period (or secular) effects may limit the application of the results to more recently born groups. Also longitudinal studies are beset with some degree of attrition. Practically, BCs benefit from a relatively stable population, considerable financial support, and the ability to link records across population-based registers. For these reasons, BCs are currently restricted to developed countries. Furthermore, like studies using other design, BC studies have not examined protective factors that reduce to the risk of mental disorders, a need recently highlighted by Patel and Goodman.[117]

Thus, apart from focusing more on comparing developmental trajectories based on individual measures (rather than group means),[39,45] future BC studies could play a pivotal role in identifying both protective and promotive factors influencing the transition from vulnerability to psychosis. This would complement the important work conducted in high-risk cohorts.[110,111] Typically, BCs are rich with data, with a wide range of variables from many different domains collected over many years. The variables are usually selected to cover health and development in general, not psychotic disorders. Thus, BC lend themselves to more integrative and sweeping models and analyses. For example, Isohanni et al[110] have proposed a lifespan model of causation which encompasses biological, social, and psychological elements and which can capture the interplay between multiple risk factors over time, mapping out of a life course. These models incorporate such elements as cumulative insults over the life course, critical periods of susceptibility throughout life, and interaction between early and late factors. Such models are transforming our understanding of chronic physical disorders[118] and can enhance the discoveries emerging from genetics. The ability to examine both genetic factors and a wide range of environmental exposures prior to the onset of the illness provides a powerful discovery platform for gene by environment studies. For example, BCs have been able to link particular genetic susceptibilities (eg, polymorphism in the 5-HTT gene), with related exposures (stressful life events) and later depression.[119]

While some environmental risks can be modeled at the individual level (eg, exposure to an infectious agent), other factors are best examined at the level of the family, neighborhood, or society.[120,121] Multilevel studies can capture both ecological level variables (eg, a neighborhood marker of social capital or poverty) and individual level variables (eg, experience-sampling methodology to assess changes in individual stress levels). Developments in statistical modeling may help this endeavor. For example, multilevel regression has been used to examine the effects of both individual and community socioeconomic variables on risk of schizophrenia in a BC study.[122]

We can expect more BC publications on schizophrenia in the decades to come. New BCs include the 1970 British BC Study,[123] the Avon Longitudinal Study of Parents and Children study in Britain (commenced 1991–1992),[124] the Danish National Birth Cohort (commenced 1996),[125] the Northern Finland Cohort 1986,[126] and the National Children's Study currently underway in vanguard centers across the United States.[127]

We have entered the new age of epidemiology of schizophrenia.[21,128] The combination of new paradigms and larger cohorts, with the tools of modern epidemiology and biomedical science, is advancing our understanding of the developmental pathways to schizophrenia. BC studies provide important insights into how the developmental trajectory of individuals who develop schizophrenia differs from their peers. BC studies provide important temporal information related to various risk factors. However, their most important contribution may lie in providing both the epidemiological context and biological samples necessary to examine the interplay of genetic and environmental factors in the etiology of schizophrenia.

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